II. Associate Power of Attorney

Prosecution of the present case has been transferred to the undersigned representative. Enclosed is an Associate Power of Attorney from Applicants' previous representative. The undersigned representative will forward a new Power of Attorney in due course, and requests that all future correspondences and communications regarding this case be directed as follows:

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III. Amendments to the Claims

The claims have been amended to place them in better form for allowance or appeal. In particular, all of the pending claims except claims 18 and 19 have been canceled without prejudice or disclaimer. Claim 18 has been amended through introduction of the language from now canceled claim 1, and thus is believed to be in better form.

New claim 47 has been introduced and is identical to claim 18, minus the complained-of term "substantially". New claim 47 is believed to simplify the issues in this regard and therefore should be an acceptable amendment after final in accordance with 37 C.F.R. § 1.116(a).

IV. Rejection of Claims Under 35 U.S.C. §112, First Paragraph

Claims 18 and 19 were first rejected under 35 U.S.C. §112, first paragraph, for what appears to be essentially two reasons. First, the position is taken that the specification does not enable "substantially" pure antigen (set forth in items 17-21 and 26-27 of the Office Action of 12/3/92), and, secondly, that the specification fails to teach the administration of a vaccine composition that inhibits cancer in a patient (items 22-25).

A separate deposit requirement with respect to claim 12 is set forth in item 28 of the Action. This rejection is believed to be moot in light of Applicants' cancellation of claim 12 without prejudice.

In response to the "substantially purified" issue, Applicants first observe that the issue is moot with respect to new claim 47, in that this claim specifies a vaccine incorporating simply a "purified" U-TAA antigen.

Regarding claim 18, it is submitted that the term "substantially purified" is appropriate to describe admittedly 100-fold purified antigen and is in no way non-enabled by the specification. The PTO apparently agrees that the specification describes and enables a U-TAA antigen preparation that is 100-fold purified over the antigen as it exists in nature (*i.e.*, as it exists in urine), but is apparently concerned with whether such an antigen preparation is "substantially" purified.

Applicants first respond by suggesting that the issue is perhaps one of semantics. The term "substantially purified" is

employed to distinguish the U-TAA antigen from naturally occurring compositions, such as U-TAA in urine or in serum. It is thus respectfully submitted that a substantially purified U-TAA antigen preparation has admittedly been prepared, in that the scope of the designation "substantially" has been defined operationally by the disclosure itself.

Applicants' position is supported by the relevant caselaw. For example, in the case of *In re Doyle*, 140 U.S.P.Q. 421 (C.C.P.A. 1964), the CCPA held that "substantial purification" of a penicillin (6-APA) can distinguish the claim from naturally occurring 6-APA. Furthermore, the use of the term "substantially" has been routinely accepted as sufficiently definite, where, as here, the specification provides an indication of what is intended by the term. See, *e.g.*, *Ex parte Smith*, 43 U.S.P.Q. 157, 158 (PTO Bd. App. 1937).

In item 27, the Action posits that Applicants are claiming a "substantially pure subunit", and thus takes the position that it must be demonstrated that the 90-100 kD subunit *per se* has been purified away from the holoantigen. In response, it is not Applicants' intention that the claims be necessarily interpreted as limited to subunit purified free of the holoantigen. A vaccine composition comprised of the purified holoantigen would fall within the scope of the pending claims, in that the subunit would nevertheless be relatively purified in such a composition, simply not purified away from the holoantigen. This intention

was made clear in Applicants' earlier response, but was not commented upon by the Examiner in the most recent Action.

In that the Action recognizes that Applicants' specification teaches at least relatively purified U-TAA antigen, there must be some means of claiming the invention of claim 18 that would be acceptable to the PTO. If the Examiner continues to reject the claim on this basis, the Examiner is respectfully requested to suggest language that would be acceptable.

The second basis of rejection under §112, first paragraph, concerns the enablement of a vaccine. The Action takes the position that Applicants' specification fails to teach inhibition of cancer with the vaccine (items 22-24 of the Action), and also fails to demonstrate immunization with a substantially purified material (item 25 of the Action).

In response, it is respectfully submitted that the Action's concerns are inapplicable to the present claims, and that the Action nevertheless fails to consider specific applicable teachings in the specification

First of all, with respect to the concerns raised in items 22-24 of the Action, it is pointed out that none of the pending claims specify cancer treatment *per se*, and thus do not require a demonstration of successful cancer treatment to support the utility requirement.

Furthermore, the specification describes the preparation of purified U-TAA antigen subunit compositions at pages 22 - 23 and at pages 33-34. Following the description of the preparation of

purified U-TAA on pages 22-23, it is stated that purified U-TAA antigen prepared in this fashion was used as a standard or target in immunoassays and "as immunogen for production of xenoantibody and murine monoclonal antibody." (page 23, lines 7-10).

An exemplary vaccine preparation is described, *e.g.*, at page 24 (". . . 100 ug U-TAA mixed with an equal volume of Mylanta (Stuart Pharmaceuticals . ."), and its use in an immunization protocol is described beginning at page 24, line 26 (" . . . four injections of U-TAA over the course of 6 weeks . . .").

Another U-TAA vaccine formulation and its use is described at page 28 (Example V), where vaccines incorporating 75 ug of purified U-TAA in PBS were administered on days 0, 15 and 28 in the preparation of hybridomas.

It is respectfully submitted that these portions of the specification more than adequately teach exemplary U-TAA vaccine preparation and use.

V. Rejection of Claims 18 and 19 As Anticipated by Brown *et al.*

The last remaining rejection of pending claims 18 and 19 is on the basis of anticipation over the Brown *et al.* publication, UK application 2,188,637. It is the Examiner's position the Brown *et al.* discloses p97, which is purported to be indistinguishable from the U-TAA of the claims.

Applicants respectfully traverse. Applicants provide herewith what is submitted to be conclusive evidence that Brown *et al.*'s p97 is an entirely distinct antigen from the U-TAA of

the present invention. Enclosed is the declaration of Dr. Rishab Gupta, one of the co-inventors of the present case, which sets forth immunological studies comparing U-TAA to, among other things, Brown *et al.*'s p97 antigen. As explained by Dr. Gupta, U-TAA was subjected to a standard Western blot analysis using one of 53 murine monoclonal antibodies reactive against other putatively distinct tumor associated antigens (see Table 1). The various anti-tumor antigen antibodies used in these studies were obtained from either the listed author of the journal article describing the respective antigen, or from commercial sources, as indicated in Dr. Gupta's Table 1.

As can be seen from Table 1, none of the 53 murine monoclonal antibodies developed by various other investigators reacted with U-TAA. However, under similar conditions, monoclonal antibody AD1-40F4, at 1:500 dilution of ascites, showed positive reaction with U-TAA. Mab AD1-40F4 is an IgM monoclonal antibody having reactivity for UTAA, described in the patent specification in Examples V, VI and VII (pages 28-31). This demonstrates that none of the monoclonal antibodies tested recognized an epitope present on UTAA.

It is particularly noteworthy and relevant to point out that in the above-described studies set forth in Table 1, two different anti-p97 antibodies, designated Mab 96.5 and Mab 118.1, were obtained from the Brown *et al.* group (Bristol-Myers), authors of the above-referenced Brown *et al.* publication. Neither of the anti-p97 antibodies obtained from the Brown *et al.*

group reacted with UTAA. From this demonstration it can be said that the claimed UTAA of the present invention is distinct from the p97 of Brown *et al*.

Based on the foregoing studies, it is respectfully submitted that the claimed UTAA has been clearly shown to be distinct from the p97 antigen of Brown *et al*. Applicants therefore submit that a withdrawal of the rejection over Brown *et al*. is appropriate.

VI. Conclusion

The present response is intended to be a complete response to the referenced Official Action. If the Examiner has any questions or comments, or suggestion as to how to progress the present case toward allowance, the Examiner is requested to contact the undersigned Applicants' representative.

Respectfully submitted,

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Date: June 3, 1993

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